Clinical review

Prevention and early detection of vascular complications of diabetes

Sally M Marshall, Allan Flyvbjerg

Diabetes reduces life expectancy by five to 10 years. Premature cardiovascular disease is the most common cause of morbidity and mortality, but the microvascular complications specific to diabetes (box 1) are also contributory factors. Diabetes is the most common reason for renal replacement therapy worldwide, the most common cause of blindness in the under 65s, and the most common cause of non-traumatic amputation. With our current knowledge, most of these devastating events could be prevented or delayed, or their impact minimised. This review focuses on the prevention, early detection, and initial management of the vascular complications of diabetes in adults.

Summary points

- Patients with diabetes have an average reduction in life expectancy of five to 10 years, mainly because of premature cardiovascular disease
- The microvascular complications specific to diabetes (retinopathy, nephropathy, neuropathy) also contribute to premature mortality and morbidity
- The risk of vascular complications can be greatly reduced by tight control of glucose and blood pressure and by aggressive management of cardiovascular risk factors
- Early detection of complications, by systematic annual screening, allows prompt intervention that may prevent or delay the emergence of end stage disease
- A multifactorial approach to tightening the management of risk factors reduces the progression of microvascular and macrovascular complications

Diabetes Research Group, Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne NE2 4HH

Sally M Marshall *professor of diabetes*

University of Aarhus, Denmark, DK 8000

Allan Flyvbjerg *professor in experimental medical research*

Correspondence to: S M Marshall s.m.marshall@ncl.ac.uk

BMJ 2006;333:475–80

Why are the complications of diabetes important?

Complications are common and the cost to the individual and society is enormous. The onset of complications reduces quality of life, particularly when both microvascular and macrovascular disease are present.[w1] The CODE-2 study gathered data on 7000 people with type 2 diabetes from eight European studies—72% had at least one complication and 24% had both (microvascular and macrovascular) complications.[w2] Over six months, 13% of the patients were admitted to hospital for a mean of 23 days. The estimated average yearly cost per patient was €2834 (£1934, $3585); 55% of this cost was attributable to hospital admissions and only 7% to the cost of insulin and oral drugs for lowering glucose.[1]

Who develops complications?

The risk of developing complications is variable (table 1). For nephropathy, in particular, a strong but unknown genetic influence exists. The duration of diabetes, glycaemic control, and hypertension are the strongest risk factors for microvascular disease; smoking, blood pressure, lipids, and albuminuria are the strongest risk factors for macrovascular disease.

Macrovascular disease

Excess mortality from cardiovascular disease is seen in all age groups, particularly in young people with type 1 diabetes (box 2), and is exacerbated by social deprivation (table).[w3] Premenopausal women with diabetes lose their protection against macrovascular disease (fig A on bmj.com).[2 w4 w5] In type 2 diabetes, the risk of myocardial infarction and stroke is two to five times higher than in the general population.

Retinopathy

The World Health Organization estimates that diabetic retinopathy is the cause of blindness in 5% of blind people worldwide.[3] Almost everyone with diabetes has some degree of retinopathy after 20 years (see appendix on bmj.com for the grading of diabetic retinopathy), but only 20-50% of patients develop sight threatening disease. In some centres the cumulative incidence of sight threatening retinopathy is falling.[4 w6 w7]

Nephropathy

About half of patients with diabetes develop microalbuminuria at some point. Approximately one third will progress to proteinuria, one third will remain microalbuminuric, and one third will revert to normal albumin excretion (fig 1).[w8] Microalbuminuria and

P+ *An appendix, extra references, and extra figures are on bmj.com. A long version of this paper is also on bmj.com*

Box 1: Long term vascular complications of diabetes

Microvascular complications
- Retinopathy
- Nephropathy
- Neuropathy

Macrovascular complications
- Cerebrovascular disease
- Ischaemic heart disease
- Peripheral arterial disease

proteinuria are more common in ethnic minorities worldwide.[w9 w10] Once proteinuria is present, progression to end stage renal disease is inevitable. From 20% to 50% of patients who start renal replacement therapy have diabetes.[5 w11] The rapid increase in the numbers of patients with diabetes requiring renal replacement in Europe in recent years is due mainly to the rise in the number of patients with type 2 diabetes (fig B on bmj.com).[6]

Neuropathy

Patients with diabetes have a 30-50% lifetime risk of developing chronic peripheral neuropathy (box 3), and 10-20% of patients develop severe symptoms.[7 w12 w13] Peripheral neuropathy contributes to foot ulceration and amputation of lower limbs.[8] Erectile dysfunction occurs in up to 50% of men over 50 years, compared with 15-20% of men without diabetes. Other neuropathies are rare but have a major impact on quality of life and life expectancy.

Pathophysiology

Both the metabolic and haemodynamic abnormalities of diabetes contribute to the development of complications. Intracellular hyperglycaemia develops in cells that cannot downregulate the uptake of glucose. This stimulates biochemical and haemodynamic pathways (fig 2). Signalling molecules and growth factors are activated, with consequent tissue damage.[9] Genetic factors and external "accelerators" also contribute. A mechanism that links the activation of these pathways to the overproduction of superoxide by the mitochondrial electron transport chain has been suggested.[10]

Microvascular complications are strongly associated with cardiovascular disease. A familial or genetic process may influence the development of both cardiovascular disease and microvascular pathology.[w14-w16]

Table 1 Risk factors and markers for the development of complications of diabetes

Factors	Microvascular disease	Macrovascular disease
Non-modifiable		
Genetic (susceptibility or protective)	++	++
Ethnic origin	+	+
Duration of diabetes	++	+
Modifiable or potentially modifiable		
Glycaemic control	++	+
Blood pressure	++	++
Blood lipids	+	++
Smoking	+	++
Body mass index or waist to hip ratio	+	+
Other microvascular complications	+	+
Cardiovascular complications	+	+
Social deprivation	+	+
Novel risk markers		
Markers of inflammation (such as C reactive protein)	+	+
Markers of endothelial dysfunction (such as von Willebrand factor)	+	+

+=Moderate risk factor or marker; ++=strong risk factor or marker.

Sources and selection criteria
- We searched PubMed with the keywords "diabetic complications", "retinopathy", "diabetic nephropathy", "microalbuminuria", "diabetic foot", "peripheral neuropathy", "cardiovascular disease", "ischaemic heart disease", "peripheral arterial disease", and "cerebrovascular disease". We gave preference to original articles published within the past three years and to reviews in journals with a high impact factor (rate of citation)
- We searched the Cochrane database of systematic reviews; Cochrane database of abstracts and reviews of effectiveness; and Cochrane central registry of controlled trials
- We searched personal archives of references

How do I prevent complications?

Box 4 lists the main strategies to prevent the complications of diabetes.

Glucose control

The diabetes control and complications trial (DCCT) in type 1 diabetes and the UK prospective diabetes study (UKPDS) in type 2 diabetes showed that the lower the glycated haemoglobin achieved the lower the risk of microvascular complications.[11 12] During the eight year open follow-up of the DCCT cohort, glycated haemoglobin values were similar in patients who had previously been managed intensively or conventionally.[13 14 w17] Despite this, patients who had previously been in the intensively managed group were less likely to have microvascular complications (fig 3). Thus, a period of good glycaemic control reduces the risk of complications for longer than the duration of tight control, a phenomenon known as metabolic memory.

The association between glucose control and cardiovascular disease is less strong but is still important. UKPDS found a 14% reduction in the risk of myocardial infarction for each 1% reduction in gly-

Box 2: Macrovascular disease in diabetes
- Macrovascular disease is the main cause of death in type 1 and type 2 diabetes
- Excess mortality is seen in all age groups, especially the young
- Premenopausal women lose their protection against macrovascular disease
- Disease is diffuse, distal, and affects many vessels
- Reocclusion and reinfarction rates are higher after thrombolysis
- Restenosis rates are higher after angioplasty, although drug eluting stenting may help
- Five year survival after coronary artery bypass grafting is lower than in non-diabetic patients

Box 3: Neuropathies in diabetes

Peripheral neuropathies
- Distal symmetric sensorimotor neuropathy
- Femoral neuropathy (amyotrophy)
- Mononeuropathies (ocular or truncal)
- Pressure palsies (median, ulnar, or lateral popliteal)

Autonomic neuropathy
- Postural hypotension
- Bladder dysfunction
- Gastric paresis
- Constipation or diarrhoea, or both
- Gustatory sweating (on the forehead, face, scalp, and neck after eating)
- Erectile dysfunction

cated haemoglobin.[w18] In the long term follow-up of DCCT, the risk of a cardiovascular event was 42% lower in the intensively managed group (fig C on bmj.com).[15]

Blood pressure

In UKPDS, tight control of blood pressure (144/82 *v* 154/87 mm Hg) reduced the incidence of a microvascular event by 37%.[16] A reduction in systolic blood pressure of 10 mm Hg was associated with a 13% reduction in risk for a microvascular event and an 11% reduction for myocardial infarction.[w19] Other studies have shown that the reduction in relative risk is at least as great in the diabetic population as in the non-diabetic population, so that the absolute benefits of a reduction in blood pressure are greater.[17 18]

The choice of initial antihypertensive drug is less important than reducing blood pressure. Tight targets (<130/80 mm Hg) are difficult to reach and require at least three antihypertensive drugs. Drugs that are taken once daily and that have good 24 hour cover should be used.

A Cochrane review suggests that angiotensin converting enzyme inhibitors are the best drugs to prevent microalbuminuria and nephropathy.[19 w20] A recent meta-analysis that did not support this conclusion has been criticised for many reasons.[w21]

Lipids

Two placebo controlled trials have shown that treatment with statins reduces the risk of a major cardiovascular event by 37% in patients with type 2 diabetes without clinically apparent cardiovascular disease.[20 21] The reduction in relative risk is as great in the diabetic population as in the non-diabetic population, so that the absolute benefit is greater.[22] Thus, all patients with diabetes aged 40 years or more should be offered statins. Younger patients have a high lifetime risk of cardiovascular disease even though their 10 year risk is relatively low. Statins should be offered to those at particularly high risk (box 4).

When fibrates should be prescribed is unclear. In a recent large, randomised, controlled trial, fenofibrate

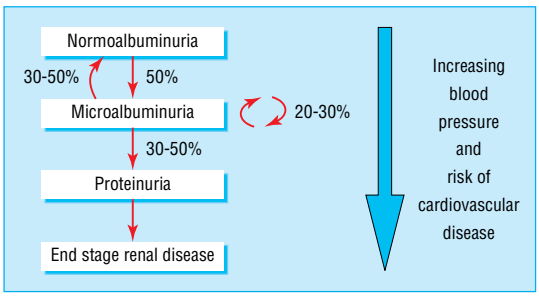

Fig 1 Development of nephropathy

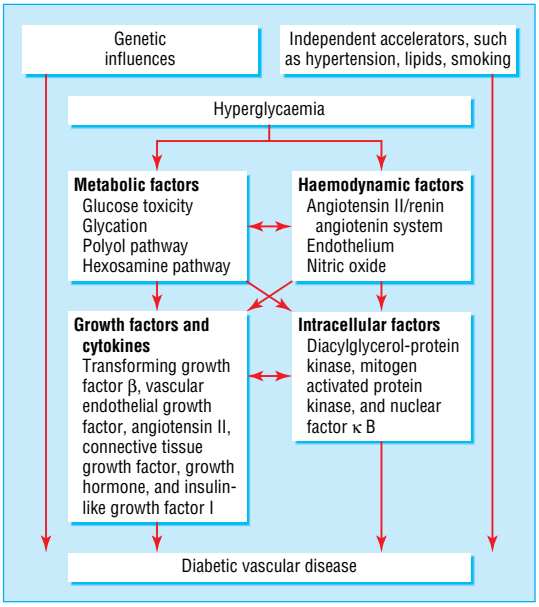

Fig 2 Metabolic pathways that contribute to vascular complications of diabetes

Box 4: Preventing complications

Glucose control
- Glycated haemoglobin should be as low as possible (but avoid undue hypoglycaemia)—aim for <7.0% if the patient is on insulin or <6.5% if not on insulin

Blood pressure

Blood pressure should be as low as possible (avoiding symptoms of postural hypotension)—aim for <130/80 mm Hg or <125/75 mm Hg if proteinuria is present, if the glomerular filtration is <60 ml/min/1.73 m^2, or if the patient has cardiovascular disease

Lipids
- Statins should be prescribed for patients over 40
- Statins should be prescribed for patients under 40 who have microvascular or macrovascular complications, hypertension, metabolic syndrome, or a strong family history of cardiovascular disease
- Total cholesterol should be <4.5 mmol/litre
- Low density lipoprotein-cholesterol should be <2.5 mmol/litre
- Fibrates should be prescribed if triglycerides are >2.3 mmol/litre and low density lipoprotein-cholesterol values are <2.5 mmol/litre

Aspirin
- Aspirin should be prescribed for all patients over 40

Smoking
- Patients should be encouraged to stop smoking

Lifestyle
- Patients should be encouraged to lose weight if necessary, exercise, and eat healthily

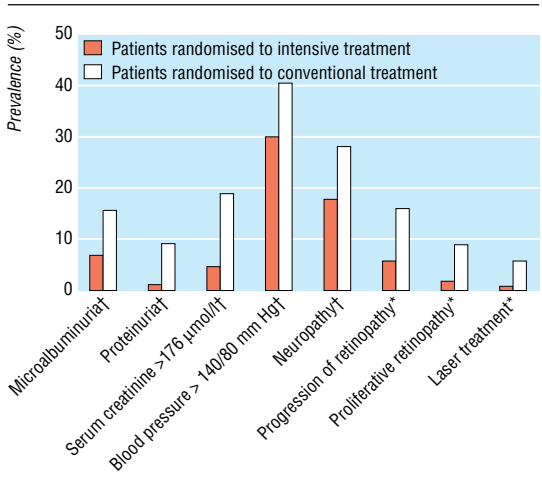

Fig 3 Prevalence of complications at open follow-up of patients who completed the diabetes control and complications trial. Prevalence of progression at *four years and †eight years

did not reduce the risk of primary coronary events in type 2 diabetes.[23] Despite the lack of robust evidence, however, once low density lipoprotein-cholesterol and control of blood glucose are optimal, clinicians should consider adding a fibrate to statin therapy if triglycerides are still greater than >2.3 mmol/litre.

Smoking

It is essential that patients stop smoking to reduce the risk of cardiovascular disease and probably the risk of microvascular complications.

Aspirin

Although no studies have been performed on primary prevention of cardiovascular disease in diabetes, low dose aspirin is usually recommended, even in the absence of overt cardiovascular disease.

How do I detect and screen for complications?

Complications must be diagnosed early—prompt intervention may prevent or delay the emergence of end stage disease such as blindness, the need for renal replacement therapy, or amputation. A systematic, structured screening programme, run annually, is most cost effective as a "one stop" package.

Macrovascular disease

Screening for macrovascular disease rests on symptoms of angina or claudication and with a low threshold for investigation. Routine exercise tolerance testing or stress echocardiography are not recommended. A 12 lead resting electrocardiogram has low sensitivity and specificity, although it does provide a useful baseline.

Table 2 Classification of chronic kidney disease

Stage	Description
1	Normal glomerular filtration rate (>90 ml/min/1.73 m^2) with other evidence of kidney disease*
2	Mild impairment: glomerular filtration rate 60-90 ml/min/1.73 m^2 with other evidence of kidney disease*
3	Moderate impairment: glomerular filtration rate 30-59 ml/min/1.73 m^2
4	Severe impairment: glomerular filtration rate 15-29 ml/min/1.73 m^2
5	Established renal failure: glomerular filtration rate <15 ml/min/1.73 m^2 or on dialysis

*Other evidence of kidney disease: microalbuminuria, persistent proteinuria, persistent haematuria after exclusion of all other causes, structural abnormalities of the kidney on ultrasound, or biopsy confirmed glomerular nephritis.

Box 5: Screening for peripheral neuropathy and peripheral arterial disease

- Inquire about symptoms of peripheral neuropathy and peripheral vascular disease
- Ask about previous foot ulceration or amputation
- Ask about physical or visual difficulty in self management of foot care
- Inspect feet for evidence of deformity, neuropathy, ischaemia, infection
- Detect neuropathy with a 10 g monofilament or 128 Hz tuning fork or biosthesiometer. Use non-traumatic pin prick testing
- Assess arterial circulation by measuring dorsalis pedis and posterior tibial foot pulses; measure Doppler ankle: brachial pressure ratio if available

Retinopathy

Corrected visual acuity should be measured and retinopathy assessed. Retinal photography, usually through dilated pupils and performed and interpreted by trained healthcare professionals, is the preferred method. Sensitivity and specificity must be acceptable, there must be an ongoing quality assurance programme, and the number of images that cannot be graded must be low.[w22] Screening with static or "mobile" cameras can be performed in the community; the retinal images are read on site or at a distant centre.

Nephropathy

Urine albumin and serum creatinine should be measured annually (fig 4). Positive urine samples should be repeated at least twice. Trends in albumin excretion with time are important. An estimated glomerular filtration rate is a better reflection of glomerular filtration than serum creatinine. Laboratories in the United Kingdom now do such estimations automatically, and web based calculators are available. Table 2 shows the agreed classification of renal disease based on estimated glomerular filtration rate.

Neuropathy and peripheral arterial disease

Box 5 shows what needs to be done to identify the four classic risk factors for developing diabetic foot

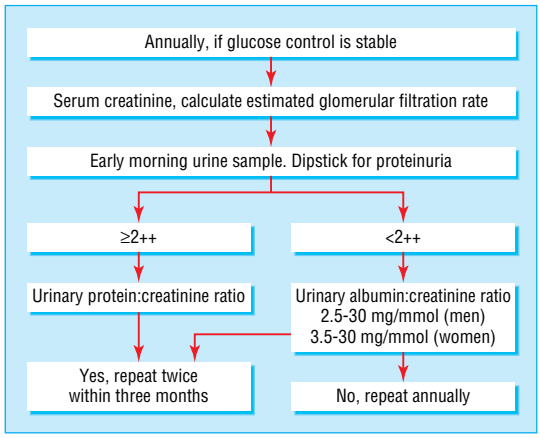

Fig 4 Screening for diabetic nephropathy

Table 3 Urgency of referring patients with diabetic retinopathy to the ophthalmology department

Problem	Time within which patient should be seen by ophthalmologist
Sudden loss of vision	Same day
Retinal detachment	Same day
New vessel formation	2 weeks
Vitreous or preretinal haemorrhage	2 weeks
Rubeosis iridis	2 weeks
Hard exudates within 1 disc diameter of fovea	12 weeks
Clinically important macular oedema	12 weeks
Unexplained retinal findings	12 weeks
Severe non-proliferative disease	12 weeks

Adapted from National Screening Programme for Diabetic Retinopathy workbook, version 3 (www.nscretinopathy.org.uk).

problems (deformity, neuropathy, ischaemia, and infection).[24] Questions should be asked about erectile function. Tests of autonomic function are not performed routinely.

How do I manage early complications?

General

Tight control of blood glucose and blood pressure reduces the risk of progression of background diabetic retinopathy to sight threatening disease and the progression of neuropathy.[11 12 16] The effect of glucose control on progression of nephropathy is less certain. Blood pressure and lipid control are extremely important.

Cardiovascular disease

Most importantly, all patients with symptoms that might reflect vascular disease, particularly ischaemic heart disease, should be investigated. The absolute benefits of treatment with statins in secondary prevention of vascular disease are greater in people with diabetes.[22]

Retinopathy

Frequent retinal examination may be required, with referral to the ophthalmology department when sight threatening disease is apparent (table 3).

Nephropathy

All patients should be prescribed a long acting, once daily angiotensin converting enzyme inhibitor or angiotensin receptor blocker titrated up to the maximum recommended or tolerated dose.[w23-w26] Additional antihypertensives should be used to achieve tight control of blood pressure. A target of 125/75 mm Hg is recommended for patients with proteinuria or an estimated glomerular filtration rate less than 60 ml/min/1.73 m^2, although these guidelines are not evidence based. Combining an angiotensin converting enzyme inhibitor with an angiotensin receptor blocker or adding an aldosterone antagonist further reduces urine albumin excretion and blood pressure in the short term.[w27-w29] However, long term benefits are unclear. Box 6 lists the indications for referral to the nephrology department.

Box 6: Indications for referring patients to the nephrology department

- The glomerular filtration rate is <45 ml/min/1.73 m^2 (if possible, refer when <60 ml/min/1.73 m^2) or serum creatinine is >150 µmol/litre
- The estimated glomerular filtration rate falls by more than 20% each year
- Presence of nephrotic syndrome
- The diagnosis is unclear
- Blood pressure is uncontrolled
- Haemoglobin is <100 g/litre and other causes have been excluded
- Presence of abnormalities in bone chemistry

Table 4 Benefits of multifactorial intervention[25]

Complication	Hazard ratio (95% confidence interval)
Cardiovascular disease	0.47 (0.24 to 0.73)
Nephropathy	0.39 (0.17 to 0.87)
Retinopathy	0.42 (0.21 to 0.86)
Autonomic neuropathy	0.37 (0.18 to 0.79)

Neuropathy and peripheral arterial disease

Patients whose feet have a high risk of ulceration or gangrene need support and education about foot care; they also need to be given prophylactic foot care and special footwear.[24] These measures can reduce amputation rates by 30-50%.[w30 w31] Early referral of patients with ulcers (and those who have had ulcers in the past) to a specialist multidisciplinary team is essential.

Support and counselling should be available for men with erectile dysfunction. Investigations to exclude other causes (measurement of prolactin, follicle stimulating hormone, luteinising hormone, testosterone, and sex hormone binding globulin) may be necessary. Oral phosphodiesterase type 5 inhibitors are effective in about 60% of men with diabetes, less than in the non-diabetic population. Alternatives include sublingual apomorphine, intraurethral drugs, intracavernosal drugs, vacuum devices, and penile prostheses.

The importance of multifactorial care

A small randomised controlled trial of patients with type 2 diabetes, microalbuminuria, and hypertension showed the importance of a structured, protocol driven, multifactorial approach to managing the complications of diabetes.[25] The intensively managed group received lifestyle advice, aspirin, and angiotensin converting enzyme inhibitors, with tight targets for glucose, blood pressure, and lipids in a specialist setting. The conventionally managed group received usual structured care in a primary care setting. Over eight years, the risks of progression of microvascular and macrovascular disease were reduced by 40-60% in the intensively managed group (table 4).

How well are we doing?

Targets are not being met and drugs are not being prescribed appropriately in most patients with diabetes worldwide.[w32 w33] Screening programmes for retinopathy and nephropathy are patchy or non-existent.[w34 w35] In the UK, the uptake for retinal screening was 57.3% in 2005 (www.yhpho.org.uk). Patients find it difficult to comply with lifestyle advice, attendance for screening, and drugs,[w36 w37] and those with most difficulty have worse outcomes.[w38 w39]

Additional educational resources

Diabetes UK (www.diabetes.org.uk)

American Diabetes Association (www.diabetes.org)

International Diabetes Federation Clinical Guidelines Task Force. *Global guidelines for type 2 diabetes*. Brussels: International Diabetes Federation, 2005 (www.IDF.org)

European Union-Austrian conference on prevention of type 2 diabetes (www.diabetesconference.at)

The Finnish development programme for the prevention and care of diabetes in Finland (www.diabetes.fi/english/programme)

National service framework for renal services part 2. *Chronic kidney disease, acute renal failure and end of life care*. London: Department of Health 2005 (www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPAmpGBrowsableDocument/fs/en?CONTENT_ID=4102941&chk=aKHxDl)

National Screening Committee. *Diabetic retinopathy screening workbook: guidance on setting up a systematic programme* (www.nscretinopathy.org.uk)

Quality Outcomes Framework. Results for England 2004/5 (www.icservices.nhs.uk)

How can we improve?

Many changes are needed to prevent the complications of diabetes and minimise their impact. Under the auspices of the Austrian presidency, the European Union has developed a national plan of action for care in diabetes (www.diabetesconference.at), and such a plan has already been enacted in Finland (www.diabetes.fi/english/programme).

The most successful interventions include many components of care contained within the chronic care model,[w40 w41] as described recently for foot care[26]:

- Organisation of care
- Clinical information systems
- Support for clinical decisions
- Delivery of care
- Support for self management.[26]

Many examples of novel ways of improving outcomes exist. In the UK, the "payment by results" scheme of the primary care quality outcomes framework has resulted in many practices reaching the specified targets (www.icservices.nhs.uk). Overall, practices attained 93.2% of the total available points for diabetes. Appreciable benefits are likely to be seen as the targets for glycated haemoglobin, lipids, and blood pressure values are tightened.

SMM is guarantor. Both authors contributed equally to preparing and writing this review.

Competing interests: SMM received payment from Novo-Nordisk for organising educational events and for attending conferences. She was a member of the International Diabetes Federation Clinical Guidelines Task Force. AF has been paid by Abbott Denmark, Astra Zenica R&D, GlaxoSmithKline Denmark, Novo-Nordisk A/S Denmark, Pfizer Denmark, Roche Pharmaceuticals, and Sanofi-Aventis/Bristol-Myers Squibb Denmark for speaking at educational programmes for nurses and doctors. He has served as a consultant for Pfizer International, Roche Pharmaceuticals, Sanofi-Aventis/Bristol-Myers Squibb Denmark, and Taisho Pharmaceuticals.

1 Jonsson B. CODE-2 advisory board. Revealing the cost of type II diabetes in Europe. *Diabetologia* 2002;45:S5-12.
2 Laing SP, Swerdlow AJ, Slater SD, Botha JL, Burden AC, Waugh NR, et al. The British Diabetic Association cohort study II: cause-specific mortality in patients with insulin-treated diabetes mellitus. *Diabetic Med* 1999;16:466-71.
3 Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, et al. Global data on visual impairment in the year 2002. *Bull World Health Organ* 2004;82:844-51.
4 Rossing P. The changing epidemiology of diabetic microangiopathy in type 1 diabetes. *Diabetologia* 2005;48:1439-44.
5 US Renal Data System. *USRDS 2005 annual data report*. Bethesda, MD: National Institute of Health, National Institute of Diabetes, Digestive and Kidney Disease, 2005 (www.usrds.org/adr.htm).
6 Van Dijk PC, Jager KJ, Dtengel B, Gronhagen-Riska C, Feest TG, Briggs JD. Renal replacement therapy for diabetic end-stage renal disease: data from 10 registries in Europe (1991-2000). *Kidney Int* 2005;67:1489-99.
7 Tesfaye S, Kempler P. Painful diabetic neuropathy. *Diabetologia* 2005;48:805-7.
8 Boulton AJM, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. *Lancet* 2005;366:1719-24.
9 Schrijvers BF, De Vriese AS, Flyvbjerg A. From hyperglycemia to diabetic kidney disease: the role of metabolic, hemodynamic, intracellular factors and growth factors/cytokines. *Endocr Rev* 2004;25:971-1010.
10 Brownlee M. The pathobiology of diabetic complications. A unifying mechanism. *Diabetes* 2005;54:1615-25.
11 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.
12 UK Prospective Diabetes Study. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 1998;352:837-53.
13 Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the epidemiology of diabetes interventions and complications (EDIC) study. *JAMA* 2003;290:2159-67.
14 Martin CL, Albers J, Herman WH, Cleary P, Waberski B, Greene DA, et al, DCCT/EDIC Research Group. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. *Diabetes Care* 2006;29:340-4.
15 Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643-53.
16 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. UKPDS 38. *BMJ* 1998;317:703-13.
17 Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al, ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethazide as required, in the Anglo-Scandinavian cardiac outcomes trial-blood pressure lowering arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;366:895-906.
18 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomised to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA* 2002;288:2981-97.
19 Strippoli GF, Craig M, Craig JC. Antihypertensive agents for preventing diabetic kidney disease. *Cochrane Database Syst Rev* 2005;4:CD004136.
20 Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
21 Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al, CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the collaborative atorvastatin diabetes study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685-96.
22 Costa J, Borges M, David C, Vaz Carneiro A. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. *BMJ* 2006;332:1115-24.
23 Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al, FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes (the FIELD study): randomised controlled trial. *Lancet* 2005;366:1849-61.
24 National Institute for Clinical Excellence. *Clinical guideline 10; type 2 diabetes. Prevention and management of foot problems*. National Institute for Clinical Excellence 2004 (www.NICE.org.uk/CGO10NICEguideline).
25 Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383-93.
26 Reiber GE, Raugi GJ. Preventing foot ulcers and amputations in diabetes. *Lancet* 2005;366:1676-7.

doi 10.1136/bmj.38922.650521.80